REMARKS

Claims 29-37, 39 and 41-46 are pending in this application. Claims 1-28, 38 and 40 have been canceled without prejudice to or disclaimer of the subject matter contained therein. Claims 29 and 35 have been amended.

Claims 1-28, 38 and 40 have been previously canceled without prejudice or disclaimer, and claims 29 and 35 have been amended, for the sole reason of advancing prosecution. Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 29 has been amended to recite "A method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentration among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a

binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step." Support for the amendment to claim 29 can be found throughout the specification and claims as originally filed. For example, please *see* page 4 lines 22-23, page 14 lines 18-20, Example 1, page 21, line 6-page 22, line 17, and Table 2 of the corresponding PCT application.

Claims 35 have been amended to correct minor typographical errors. Support for the amendment to claims 35 can be found throughout the specification and claims as originally filed.

The specification has been amended to include a brief description of each drawing figure in the application as well as to properly reference each of the same throughout the specification.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. Interview

Applicants kindly thank Examiner Lam for the interview conducted between the Examiner and Applicants' undersigned representative. During the interview, the Examiner indicated that the final Official Action dated December 4, 2009 was issued in error as the amendment filed on August 21, 2009 was not intended to be responsive to the Official Action dated August 6, 2009. Accordingly, the Examiner indicated that the final Official Action dated December 4, 2009 has been withdrawn; therefore, Applicants must respond to the non-final Official Action dated August 6, 2009. Accordingly, Applicants note that this paper is, in fact, responsive to the non-final Official Action dated August 6, 2009.

II. At page 2 of the Official Action, the specification has been objected to.

The Examiner objects to the specification because there is no brief descriptions of various figures. As discussed above, the specification has been amended to describe the drawing figures by reference to each separate drawing figure. Applicants submit that, as amended herein, the specification now contains brief descriptions for each of the drawing figures in the present application. Accordingly, Applicants request that the Examiner reconsider and withdraw this objection.

III. At page 2 of the Official Action, claims 29 and 37 have been objected to.

The Examiner objects to claims 29 and 37 because allegedly "there needs to be more than one member for there to be simultaneous adsorbing." *See* the Official Action at page 2, claim objections.

Applicants respectfully submit that the Examiner's interpretation of the claimed subject matter is flawed. In this regard, Applicants submit that the term "simultaneously" in the portions of claim 29 and 35 that the Examiner refers to in the objection does not necessarily refer to adsorbing more than one first binding member. In contrast, the term "simultaneously" may refer to, for example, adsorbing the first binding member at the plurality of microspots and presenting the second binding member at the same time, i.e., simultaneously. Therefore, Applicant submits that the term "member" does not need to be replaced by the term "members".

Accordingly, Applicants request that the Examiner reconsider and withdraw this objection.

IV. At page 3 of the Official Action, claims 29-36 and 43-45 have been rejected under 35 USC § 112, second paragraph.

The Examiner asserts that claims 29-36 and 43-45 are indefinite because the recitation "each of the microspots located at a surface between at least two or more of the microspots" is allegedly indefinite.

In view of the following, this rejection is respectfully traversed.

Applicants submit that, as amended, claim 29 is clear and definite within the meaning of 35 USC § 112. In this regard, Applicants note that claim 29 has been amended to recite "simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots." Claim 29 no longer recites "each of the microspots located at a surface between at least two or more of the microspots." Each of claims 30-36 and 43-45 depend, either directly or indirectly, form claim 29.

Applicants submit that claims 29-36 and 43-43 are now clear and definite within the meaning of 35 USC § 112. Therefore, Applicants request that the Examiner reconsider and withdraw this rejection.

V. At pages 3-16 of the Official Action, claims 29-37, 39 and 41-46 have been rejected under 35 USC §103(a) as being obvious over various combinations of Malmqvist et al. (US Patent No. 6,200,814) in view of Newgard et al. (US Patent No. 6,110,707) and Lambert (US Publication No. 20060210984) alone, or in further view of either Kansa et al. (US Patent No. 6,478,839), Natesan et al. (US Publication No. 20020048792) or Siddigi et al. (US Patent No. 5,541,113).

he Examiner asserts that it would have been obvious to modify the subject matter described by Malmqvist et al. with the subject matter in Newgrad et al. and Lambert et al. alone, or in view of either Kansa et al. Natesan et al. or Siddigi et al. to obtain the presently claimed subject matter.

In view of the following, these rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to

combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because, whether taken alone or in combination, none of the cited references teach or suggest each and every limitation of the presently pending claims as required by *In re Wilson.*

Claim 29 is directed to a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member

at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentration among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step. Claims 29-36 and 43-46 depend, either directly or indirectly, from claim 37.

Claim 37 is directed to a method for localizing a molecular species at each of two or more microspots on a surface, comprising: activating a microspot surface by: forming a first channel around the region containing the microspot; introducing a solution containing an activating substance into the channel; and removing excess activating solution from the channel; simultaneously ***adsorbing a molecular species to each of the two or more microspots***, the adsorbing comprising forming at least two further channels, each being perpendicular to the first channel; simultaneously introducing a solution containing the molecular species into the channel; and optionally deactivating the microspot, wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and wherein the

molecular species may be adsorbed at identical or different surface densities to each of the microspots. Claims 39, 41 and 42 depend, either directly or indirectly, from claim 37.

In contrast to the presently pending subject matter, Malmqvist et al. is directed to methods and devices for controlling a fluid flow over a sensing surface within a flow cell. The methods according to Malmqvist et al. employ laminar flow techniques to position a fluid flow over one or more discrete sensing areas on the sensing surface of the flow cell. *See* Malmqvist et al. at the abstract.

However, unlike the presently claimed subject matter, Malmqvist et al. do not teach or suggest "...simultaneously presenting the second binding member ***at a plurality of concentrations*** to the first binding member ***at the plurality of microspots***, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," as recited in claim 29. In addition, Applicants submit that Malmqvist et al. do not teach or suggest ***determining a kinetic parameter without necessitating a regeneration step***.

In this regard, Applicants submit that Malmqvist et al. relates to technology owned by the assignee of the same and commercially marketed as the original Biacore™ 2000 and Biacore™ 3000 systems. In addition, Malmqvist et al. provides possible improvements to the fluid delivery system of the Biacore™ 2000 and Biacore™ 3000 systems. In Malmqvist et al. the fluid delivery system is based on a laminar flow later named "hydrodynamic addressing." Applicants submit that Malmqvist et al. adheres to a paradigm that existed at the time; that is, ***analysis of one analyte concentration over several flow cell surfaces or sensitization spots***.

Malmqvist et al. merely proposes a gradient with regard to the amount *of immobilized ligand bound* to the surface of each sensing area, where the gradient is in fact a byproduct of laminar flow. *See* Malmqvist et al. column 13, line 12 to column 14, line 37, and in particular column 14 lines 26-37. The gradient of the immobilized ligand density is not a parameter which is used in the calculation of the kinetic parameters, as recited in amended claim 29. Further, Malmqvist et al. do not teach or suggest a binding assay involving a plurality of *analyte* concentrations (being the second binding member in the subject application).

As evidence of this, Applicants submit herewith a declaration executed by Prof. Gideon Schreiber. As indicated in Professor Schreiber's declaration, ***the laminar flow technique of Malmqvist et al. is unsuitable for performing a kinetic parameter measurement as claimed***. The laminar flow (hydrodynamic addressing) method, as presented by Malmqvist et al., necessitates different flow rates to create a boundary between the flown solutions. Different flow rates might change the kinetic behavior of the interaction, and thus obtaining a full and accurate binding assay with a plurality of analyte concentrations is practically impossible with this technology.

The option of simultaneously presenting a second binding member (the binding member to the immobilized ligand) at a plurality of concentrations at the plurality of microspots is not described by Malmqvist et al., nor is it possible as previously explained. Throughout the entire text of Malmqvist et al., including all of its respective examples, a single analyte concentration is run at a time. Analysis of two or more, e.g., a plurality of analyte concentrations, would require a serial processing ***and thus necessitate regeneration between*** each run.

A post-art publication dated January 20, 2005 by Robert *Karlsson* (a Biacore researcher as Malmqvist) clearly states as follows: "...***[f]rom the prior art it may therefore be concluded*** *that for determining kinetic rates for molecular interactions using systems based on biosensors and affinity analysis,* ***it is necessary to regenerate the immobilized ligand prior to contacting the sensor surface with a different concentration of analyte to thereby present essentially one and the same ligand surface to each analyte concentration,*** unless (i) a continuous gradient of the analyte is used, or (ii) initial binding rates are determined in systems free from mass transport limitations...." *See* Karlsson et al., at page 1, paragraph 6 and paragraphs 15-16. Additionally, please see paragraph 25, of Prof. Gideon Schreiber's declaration, attached herewith.

In addition, the limitations of the Biacore technology is not only supported by their own art in which they attempt to avoid regeneration by employing completely different methodology, but also supported by other important figures in the field of molecular interaction analysis which substantiate Applicant's arguments. As evidence of this, Applicants submit herewith Roth et al., "Higher-throughput, label-free, real-time molecular interaction analysis," Analytical Biochemistry 361 (2007) 1–6.

By way of reference to Roth et al., Applicants note that at the bottom page 4, last paragraph, Roth et al. indicate that the presently claimed technology described as One Shot Kinetics (OSK), allows for "... generating a full analyte concentration series with one injection [25,26]. This reduces analysis time significantly and eliminates the need for surface regeneration." Applicants submit that this confirms that there was a need for

eliminating the need for surface regeneration that was met by the introduction of the claimed subject matter.

Therefore, Applicants submit that, the state of the art before and around January 20, 2005, and certainly before November 11, 2003, necessitated regeneration of the surface. The silence of Malmqvist et al. and the other references cited with respect to a regeneration step is not because a regeneration step was not required, but rather due to fact that prior to the present application, no one attempted to solve this problem because the focus was on providing improved selective ligand immobilization techniques (or sensitization) on the basis of the laminar flow technology.

In view of this, Applicants respectfully disagree with the Examiner's assertions that "[n]either Malmqvist et al. nor Newgard et al. nor Lambert discloses that a regeneration step is required, nor is it implied that it is required in order to carry out the disclosed methods, and thus the method discussed above as taught by these references do not necessitates a regeneration." *See* the Official Action at page 9, lines 3-7. As Prof. Gideon Schreiber's indicates in the declaration, Malmqvist et al. and the other cited references did not disclose that a regeneration step is required because it was not a problem they attempted to address. In this regard, Prof. Schreiber notes that this robust technology cannot be deduced by default.

Additionally, Applicants note that in the previous Official Action dated November 13, 2008, the examiner stated that "*That is, in standard kinetic binding interaction measurements, the second binding member (target) is removed so that another concentration of the target is contacted with the probe. Malmqvist et al., Newgard et al. and Lambert do not disclose a kinetic binding assay that does not necessitate a*

regeneration step." See the Official Action dated November 13, 2008 at page 7, lines 9-13.

In other words, for the performance of a kinetic binding assay the prior art necessitates a regeneration step. At page 7, lines 14 to page 8 of the Action dated November 13, 2009, the Examiner explains why regeneration is required.

In this regard, the Examiner explains at the bottom of pages 7-8, that determining a kinetic measurement requires the flowing of a second binding partner in different known concentrations over an immobilized ligand, a step which necessitates regeneration. Should the Examiner maintain these rejections, Applicants respectfully request that the Examiner clarify this issue.

For a more detailed discussion of the present subject matter in view of the cited art, Applicants respectfully request that the Examiner review Professor Schreiber's declaration, as well as the references cited therein. A copy of each reference discussed is also submitted herewith.

Newgard et al. do not remedy the deficiencies of Malmqvist et al. Newgard et al. is directed to a method of engineering a mammalian cell comprising providing a starting cell, introducing into the starting cell an amylin-encoding gene operatively linked to a first promoter, and selecting a cell that exhibits increased amylin production as compared to the starting cell, where the method may further comprises introducing into the selected cell an insulin-encoding gene operatively limned to a second promoter.

Like Malmqvist et al., Newgard et al. do not teach or suggest "...simultaneously presenting the second binding member ***at a plurality of concentrations*** to the first binding member ***at the plurality of microspots***, there being a plurality of combinations

of first binding member surface density and second binding member concentrations among the plurality of microspots," or ***determining a kinetic parameter without necessitating a regeneration step***, as presently claimed.

Lambert does not remedy the deficiencies of Malmqvist et al. and Newgard et al. Lambert is directed to methods for normalizing for variations in signal intensity observed in biomolecular binding assays carried out in flow cell cartridges. *See* Lambert at the abstract.

Like Malmqvist et al. and Newgard et al., Lambert does not teach or suggest "...simultaneously presenting the second binding member ***at a plurality of concentrations*** to the first binding member ***at the plurality of microspots***, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," or ***determining a kinetic parameter without necessitating a regeneration step***, as presently claimed. Accordingly, whether taken alone or in combination, Malmqvist et al., Newgard et al. and Lambert fail to teach or suggest each and every element of the presently pending claims.

None of Kansa et al., Natesan et al. or Siddigi et al. remedy the deficiencies of Malmqvist et al., Newgrad et al. and Lambert. Applicants note that Kansa et al. appears to be cited in error as Kansa et al. is directed to a device for induction-heat melting treatment of metal-oxide-powders. Natesan et al. is directed to a method for regulated production of a desired protein in cells, which comprises providing cells containing recombinant nucleic acids encoding at least one fusion protein which binds to a selected ligand, wherein the fusion protein comprises a ligand binding domain and a

DNA binding domain. Siddigi et al. is directed to a method for detecting analyte in an aqueous solution at a physiological pH, by reductive or oxidative electrochemical luminescence methodologies, which method proceeds by labeling the analyte with a transition metal complex, followed by inducing the transition metal label to luminescence by application of a suitable electrical potential to a solution containing the label and the analyte.

In contrast to the presently claimed subject matter, like Malmqvist et al., Newgard et al. and Lambert, none of Kansa et al., Natesan et al. and Siddigi et al. teach or suggest "...simultaneously presenting the second binding member ***at a plurality of concentrations*** to the first binding member ***at the plurality of microspots***, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," or ***determining a kinetic parameter without necessitating a regeneration step***, as presently claimed.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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